REMARKS

Summary of the Invention

The present invention features the discovery of the mammalian methionine synthase reductase gene. Accordingly, the invention provides wild-type and mutant mammalian methionine synthase reductase nucleic acid molecules and their complements.

Summary of the Office Action

Claims 1-5 and 35-53 are pending. Claim 3 is objected to for depending upon a rejected claim, but would be otherwise allowable. Claim 5 is objected to for lack of clarity. Claims 4-5, 35, 39-47, and 50-53 are rejected under 35 U.S.C. § 112, second paragraph, for indefiniteness. Claims 1-2, 4-5, 35-47, and 50-53 are rejected under 35 U.S.C. § 112, first paragraph, for lack of written description and lack of enablement. Claims 48 and 49 have been withdrawn from consideration. By this reply, Applicants cancel claims 35, 39-40, 44, and 50-51, amend claims 1-5, 36-38, 41-43, 45-47, and 52-53, add new claims 54-55, and address each of the Examiner's objections and rejections below.

Support for the Amendment

Support for the amendment to claims 1-5, 36-38, 41-43, 45-47, and 52-53 is found in prior claims 1-5, 35-47, and 50-53, and in the specification, e.g., at page 6, lines 1-11, page 13, line 18, through page 14, line 16, page 15, line 7, through page 16, line 18, page 18, lines 9-17, page 22, lines 14-18, and page 35, line 15, through page 38, line 18. No new matter is added by the amendment.

Formalities

Applicants have been requested to submit amended drawings that satisfy the requirements of 37 C.F.R. § 1.84. Accordingly, Applicants submit herewith 14 sheets for appropriately amended figures 1-8.

Claim Objection

Claim 5 is objected to for lack of clarity. The Examiner states that "it is suggested that the term 'at least 50% of at least 60 contiguous nucleotides" be replaced with 'at least 30 contiguous nucleotides'" (Office Action, p. 3). Applicants have amended claim 5 as suggested by the Examiner. Accordingly, this objection may now be withdrawn.

Rejections under 35 U.S.C. § 112, second paragraph

Claims 4-5, 35, 39-47, and 50-53 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failure to distinctly claim the subject matter which Applicants regard as the invention. With respect to claim 4, and claims 5, 35, and 53 dependent therefrom, the Examiner states that the "recitation of 'nucleic acid sequence that hybridizes...to a sequence'" is indefinite because "a sequence is a graphical representation of the order in which nucleotides/amino acids are arranged in a molecule. Since hybridization occurs between molecules, it is unclear as to how a sequence can hybridize to a nucleic acid" (Office Action, p. 4). The rejection of claim 35 is moot in light of Applicants' cancellation of this claim. Applicants have addressed the rejection of pending claims 4, 5, and 53 by amendment to claim 4,

which now recites that the nucleic acid molecule "hybridizes...to the polynucleotides of SEQ ID NO: 1, SEQ ID NO: 41, SEQ ID NO: 43, SEQ ID NO: 45, or SEQ ID NO: 47", as was suggested by the Examiner. Accordingly, the rejection of claims 4, 5, 35, and 53 should be withdrawn.

The Examiner also rejects claim 4, and claims 5, 35, and 53 dependent therefrom, for indefiniteness, stating that "the recitation of 'nucleic acid comprises a region complementary to a naturally-occurring mammalian methionine synthase reductase mutation or polymorphism'" is unclear because:

> in the absence of an additional structural limitation defining the area comprising the naturally-occurring mutation/polymorphism which is specific for a mammalian methionine synthase reductase polynucleotide, and/or in the absence of a limitation defining which specific mutations or polymorphisms are encompassed by the claims, it is unclear as to whether any polynucleotide which has any nucleotide in any position (polymorphism) or lacks any nucleotide fragment (deletion) and hybridizes to the polynucleotides of SEQ ID NO: 1 or 41 is encompassed by the claim. (Office Action, p. 4.)

The Examiner further states:

> For examination purposes, it will be assumed that the claim encompasses any polynucleotide which hybridizes under the recited conditions to the polynucleotide of SEQ ID NO: 1 or 41 and wherein said polynucleotide comprises a region which is completely complementary to a fragment of a mammalian methionine synthase reductase nucleic acid wherein said fragment comprises a naturally-occurring mammalian methionine synthase reductase mutation or polymorphism. (Office Action, pp. 4-5.)

Applicants have amended claim 4 so that it no longer recites the phrase "wherein said nucleic acid comprises a region complementary to a naturally-occurring mammalian methionine synthase reductase mutation or polymorphism." Instead, claim 4 now recites that the nucleic acid molecule hybridizes under the recited conditions to the polynucleotides of SEQ ID NO: 1, SEQ ID NO: 41, SEQ ID NO: 43, SEQ ID NO: 45, or SEQ ID NO: 47. Therefore, in light of the

amendment to claim 4, the rejection of claim 4, and claims dependent therefrom, should be withdrawn.

The Examiner also rejects claims 39 and 41, and claims 40, 42-44, and 51-53 dependent therefrom, for lack of clarity, stating:

> Since there is no structural limitation in regard to the naturally-occurring mammalian methionine synthase reductase mutation/polymorphism and/or which mutations or polymorphisms are included (i.e. specific substitutions, insertions, or deletions), it is unclear as to how the terms [nucleic acid comprises a naturally-occurring mammalian methionine synthase reductase mutation or polymorphism] further limit the claims. (Office Action, p. 5.)

Applicants have cancelled claim 39 and have amended claim 41 so that it no longer recites the phrase "nucleic acid comprises a naturally-occurring mammalian methionine synthase reductase mutation or polymorphism." Instead, claim 41 now recites that the nucleic acid molecule has a polynucleotide sequence that has at least 50% sequence identity to a sequence that is complementary to SEQ ID NO: 1, SEQ ID NO: 41, SEQ ID NO: 43, SEQ ID NO: 45, or SEQ ID NO: 47. Therefore, the rejection of claims 39 and 41, and claims dependent therefrom, should be withdrawn.

Applicants note that new claim 55, which depends from claims 41, 42, and 43, recites that "the complement of...[the] polynucleotide sequence [of claim 41] comprises a naturally-occurring mammalian methionine synthase reductase mutation or polymorphism." The Examiner states that, in the context of claim 41, it is unclear how this phrase further limits the claim. As would be understood by one skilled in the art, the above phrase, as it is recited in present claim 55, indicates that the mutation or polymorphism in the mammalian methionine synthase reductase gene is one that is naturally found in the MTRR gene and is not artificially

generated, such as by genetic engineering or manipulation. Therefore, the phrase is not unclear and further limits the scope of claims 41, 42, and 43, as is required by 37 C.F.R. § 1.75(c). For this reason, the rejection of claims 39 and 41 should not be applied to new claim 55, nor should it be applied to pending claim 53, which depends from claim 4, or new claim 54, which depends from claims 36, 37, and 38, as claims 53 and 54 contain the same phrase.

Claims 35, 40, and 44 rejected for lack of clarity. These claims have been cancelled. Therefore, the rejection of these claims should be withdrawn.

Claims 41-43, and claims 44-47 and 50-53 dependent therefrom, are rejected for lack of clarity. The Examiner states that the phrase "sequence that has at least #% sequence identity to the corresponding region of SEQ ID NO: 1" is unclear because "one cannot determine which corresponding region of SEQ ID NO: 1" is being referenced (Office Action, p. 6). Applicants have amended claims 41-43 so that the claims now refer to "a sequence that is complementary to SEQ ID NO: 1, SEQ ID NO: 41, SEQ ID NO: 43, SEQ ID NO: 45, or SEQ ID NO: 47". Therefore, claims 41-43 now recite that the percent identity of the nucleic acid molecule is determined by reference to the entire nucleic acid sequence of SEQ ID NO: 1, SEQ ID NO: 41, SEQ ID NO: 43, SEQ ID NO: 45, or SEQ ID NO: 47. Accordingly, the rejection of claims 41-43, and claims dependent therefrom, should now be withdrawn.

Claims 45 and 46 are rejected for lack of clarity for reciting the phrase "polypeptide having at least 20-30% of the ability to catalyze...as the methionine synthase reductase polypeptide of SEQ ID NO: 2." The Examiner states that the phrase will be interpreted as "polypeptide having at least 20-30% of the ability to catalyze...as that of the methionine synthase reductase polypeptide of SEQ ID NO: 2." Applicants have amended claims 45 and 46 to recite

the phrase "polypeptide having at least [#%] of the biological activity of the methionine synthase reductase polypeptide of SEQ ID NO: 2." Applicants believe that this amendment overcomes the rejection of claims 45 and 46 and respectfully request that the rejection be withdrawn.

The Examiner also rejects claim 47, stating:

> Claim 47 remains rejected as indefinite due to the recitation of "consensus binding site for one or more cofactors" as it is unclear which are the residues of the consensus binding site encompassed by the claims...As such, it is unclear as to how one can reasonably establish which are the consensus binding sites encompassed by the claim. (Office Action, p. 7.)

Applicants respectfully disagree with the Examiner, but in the interest of expediting prosecution of the present case, Applicants have amended claim 47 to include the limitations of cancelled claim 50 so that it now specifies that the FAD, FMN, and NADPH consensus binding sites comprise a sequence selected from any one of SEQ ID NOs: 25-40. Therefore, the rejection of claim 47 under 35 U.S.C. § 112, second paragraph, should be withdrawn.

Finally, claim 52 is rejected for lack of clarity for reciting the phrase "administration of said nucleic leads to a decrease..." The present amendment to claim 52 eliminates this phrase from the claim. Therefore, the rejection of claim 52 should be withdrawn. The phrase is now recited in present claims 4 and 41, but it has been appropriately amended to recite "administration of said nucleic acid molecule to a subject leads to a decrease in the expression of methionine synthase reductase polypeptide in said subject." Accordingly, the rejection of claim 52 should not be applied to amended claims 4 and 41.

Rejections under 35 U.S.C. § 112, first paragraph

Claims 1-2, 4-5, 35-47, and 50-53 are rejected under 35 U.S.C. § 112, first paragraph, for

lack of written description and lack of enablement. Each of these rejections is addressed separately below.

Written Description

Claims 1-2, 4-5, 35-47, and 50-53 are rejected under 35 U.S.C. § 112, first paragraph, for lack of written description. The Examiner states:

> In the instant case, the genera of nucleic acids claimed are large variable genera with the potentiality of encoding many different proteins (polynucleotides of any function), and/or having many distinct structures (any mammalian methionine synthase reductase)...Thus, Applicant's disclosure is deemed insufficient to put one of ordinary skill in the art in possession of all attributes and features of all species within the claimed genera of polynucleotides. (Office Action, pp. 10 and 11).

The Examiner cites several reasons why the claimed genus of mammalian methionine synthase reductase nucleic acid molecules do not satisfy the written description requirement of 35 U.S.C. § 112, first paragraph (e.g., lack of structure or function). Applicants address the Examiner's reasons below.

The Written Description Requirement: The Legal Standard

The written description requirement, as set forth in 35 U.S.C. § 112, first paragraph, requires that the "specification shall contain a written description of the invention." The M.P.E.P. § 2163 states:

> The written description requirement has several policy objectives. "[T]he 'essential goal' of the description of the invention requirement is to clearly convey the information that an applicant has invented the subject matter which is claimed." *In re Barker*, 559 F.2d 588, 592 n.4, 194 USPQ 470, 473 n.4 (CCPA 1977). Another objective is to put the public in possession of what the applicant claims as the invention. See *Regents of the University of California v. Eli Lilly*, 119 F.3d 1559, 1566, 43 USPQ2d 1398, 1404 (Fed. Cir. 1997), *cert. denied*, 523 U.S. 1089 (1998).

"To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention" (M.P.E.P. § 2163). Furthermore:

> The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice..., reduction to drawings..., or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus.... See *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406. (M.P.E.P. § 2163(II)(A)(3)(a)(ii).)

Applicants have plainly met this standard for the claims provided herewith.

Applicants have Satisfied the Written Description Requirement

The Examiner states that claims 1 and 2 are "directed to a genus of mammalian or human methionine synthase reductases having <u>any structure</u>", but that Applicants' specification fails to disclose "which are the critical structural elements required in any mammalian polynucleotide to encode a methionine synthase reductase" (Office Action, p. 10). Applicants have amended claim 1 to specify that the substantially pure nucleic acid molecule has at least 90% sequence identity to SEQ ID NO: 1 and encodes a mammalian methionine synthase reductase polypeptide that is capable of catalyzing the reductive methylation of methionine synthase-cob(II)alamin to generate

methionine synthase-cob(III)alamin-CH3. The present amendment finds clear basis in the specification as filed (see, e.g., page 13, line 18, through page 14, line 16, and page 18, lines 9-17, of the specification; see *In re Barker, supra*) and provides a structural and functional limitation for the presently claimed methionine synthase reductase nucleic acid molecule, which is sufficient to satisfy the written description requirement (see *Regents of the University of California v. Eli Lilly & Co., supra).* In light of the present amendment to claim 1, the Examiner's rejection of claims 1 and 2 for lack of written description should be withdrawn.

The Examiner also states that claims 4, 5, 35-44, 51-52, and 53 are directed to "a genus of polynucleotides of any function" and that the specification fails to disclose "other functions for the structural homologs of the polynucleotides of SEQ ID NO: 1 or 41 which hybridize in 2xSSC medium at 40 C as encompassed by the claims,...[or] additional naturally-occurring methionine synthase reductase mutations or polymorphisms in other mammalian or human methionine synthase reductases [in] addition to those described in the specification in regard to the human polynucleotide of SEQ ID NO: 1" (Office Action, p. 10). Applicants have cancelled claim 35, and have amended independent claims 4, 36, and 41 to recite both structural limitations (i.e., hybridization or percent identity) and functional limitations (i.e., the ability to decrease the expression of a methionine synthase reductase polypeptide or the ability to catalyze the reductive methylation of methionine synthase-cob(II)alamin to generate methionine synthase-cob(III)alamin-CH3). Clear basis for the amendments is found in the specification on, e.g., page 5, line 15, through page 16, line 11, page 15, line 23, through page 16, line 18, and page 18, lines 9-17. Claims 4, 36, and 41, as presently amended, provide relevant, identifying characteristics sufficient to show that Applicants were in possession of the claimed genus. Therefore, claims 4,

36, and 41, and claims dependent therefrom, clearly satisfy the written description requirement (see *Regents of the University of California v. Eli Lilly & Co., supra*). In addition, Applicants have amended claim 53, and have provided new claims 54 and 55, which recite that the nucleic acid molecule (claim 54) or the complement of the nucleic acid molecule (claims 53 and 55) comprises a naturally-occurring mammalian methionine synthase reductase mutation or polymorphism. These claims provide an additional characteristic of the nucleic acid molecules of present claims 4, 36, and 41, and claims dependent therefrom. Accordingly, for the foregoing reasons, the rejection of claims 4, 5, 35-44, 51-52, and 53 should be withdrawn.

With respect to claims 45 and 46, the Examiner states that these claims are drawn to mammalian methionine synthase reductases that "have a fraction of the activity of the polypeptide of SEQ ID NO: 2" and that the "structural characteristics required in any mammalian methionine synthase reductase such that they display only 20-30% or 55-75% of the activity of the polypeptide of SEQ ID NO: 2 in catalyzing the methylation of methionine synthase-cob(II)alamin" are not adequately disclosed in Applicants' specification (see Office Action, pp. 10-11). Applicants respectfully disagree.

Claims 45 and 46 recite a nucleic acid molecule that encodes a mammalian methionine synthase reductase having at least 20-30% or 55-75%, respectively, of the biological activity of the methionine synthase reductase polypeptide of SEQ ID NO: 2. The Examiner incorrectly states that these claims recite that the biological activity is only 20-30% or 55-75% of the activity of the methionine synthase reductase polypeptide of SEQ ID NO: 2. Therefore, claims 45 and 46 are directed to nucleic acid molecules that encode methionine synthase reductase polypeptides that have a reduced biological activity relative to a wild-type methionine synthase reductase

polypeptide, not nucleic acid molecules that encode methionine synthase reductase polypeptides that exhibit biological activity only within an exact range relative to wild-type methionine synthase reductase polypeptide (i.e., 20-30% or 55-75%). In other words, the polypeptides encoded by the presently claimed nucleic acid molecules could exhibit a biological activity relative to wild-type methionine synthase reductase polypeptide of greater than 20-30% or greater than 55-75%. Applicants' specification clearly teaches that a biologically-active methionine synthase reductase polypeptide includes those that "display activity equivalent to at least 20-30% of wild-type activity, more preferably, at least 35-50% of wild-type activity, still more preferably, 55-75% of wild-type activity, and most preferably, a biologically active methionine synthase reductase will display at least 80-90% of wild-type activity" (Specification, p. 16, lines 5-10). For this reason, Applicants submit that claims 45 and 46 clearly satisfy the written description requirement of 35 U.S.C. § 112, first paragraph, and the present rejection of these claims should be withdrawn.

Finally, the Examiner states that claim 47 recites a genus of polynucleotides that encode mammlian methionine synthase reductases that "comprise a consensus binding site for one or more cofactors or...comprise the polypeptide of SEQ ID NO: 25, which is disclosed as a cofactor binding site...[and that] the specification fails to disclose...the critical structural elements required in any FAD, FMN or NADPH binding site" (Office Action, p. 9). Applicants have amended claim 47 so that it now includes the limitations of prior claim 50. Applicants submit that in light of the present amendment, claim 47 now clearly recites the critical structural elements of the FAD, FMN, and NADPH consensus binding sites, which are set forth in SEQ ID NOs: 25-40. Therefore, the written description requirement of 35 U.S.C. § 112, first paragraph,

has been met (see *Regents of the University of California v. Eli Lilly & Co., supra*), and the present rejection of claim 47 should be withdrawn.

Enablement

Claims 1-2, 4-5, 35-47, and 50-53 are rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. The Examiner states that the specification is enabling for the polypeptides of SEQ ID NO: 1, 41, 42, 43, 45, and 47, but that it does not reasonably provide enablement for any mammalian or human methionine synthase reductase, a mammalian or human methionine synthase reductase of any function that is identified by hybridization to the polynucleotides of SEQ ID NO: 1 or 41 or by its sequence identify to SEQ ID NO: 1, or a polynucleotide that encodes a mammalian methionine synthase reductase having a fraction of the activity of the polypeptide of SEQ ID NO: 2 or having a consensus binding site for FAD, FMN, or NADPH. Applicants respectfully disagree, but have amended independent claims 1, 4, 36, and 41 to include a structural limitation (i.e., percent identity or hybridization conditions) and a functional limitation (i.e., the ability to decrease the expression of a methionine synthase reductase polypeptide or the ability to catalyze the reductive methylation of methionine synthase-cob(II)alamin to generate methionine synthase-cob(III)alamin-CH3) of the recited nucleic acid molecule.

Applicants submit that practicing the full scope of present claims 1, 4, 36, and 41, and claims dependent therefrom, would not require undue experimentation by one skilled in the art. As was discussed in the previous Reply to Office Action, filed on May 16, 2002, the specification teaches the use of oligonucleotide primers (see, e.g., Table 1) for amplifying and

sequencing a methionine synthase reductase nucleic acid, or a segment thereof, from a sample, such as fibroblast cells (pages 17 and 42). The skilled artisan could easily compare the sequence of the nucleic acid molecule identified using the primer(s) with any one of the sequences provided by SEQ ID NOs: 1, 41, 43, 45, and 47, to determine the sequence identity of the identified nucleic acid molecule. Furthermore, the specification clearly teaches high stringency conditions and methods that can be used by one skilled in the art to identify nucleic acid molecules that hybridize to any one of the sequences provided by SEQ ID NOs: 1, 41, 43, 45, and 47 (see, e.g., page 16, lines 19-23).

The specification also provides considerable guidance with respect to identifying whether the nucleic acid molecule encodes a biologically-active methionine synthase reductase that has the ability to catalyze the reductive methylation of methionine synthase-cob(II)alamin to generate methionine synthase-cob(III)alamin-CH3, as well as the amount of that biological activity relative to wild-type methionine synthase reductase (SEQ ID NO: 2). For example, the specification teaches that methionine synthase reductase activity can be determined by measuring the formation of $^{14}CH_3$-cob(III)alamin which results from the transfer of $^{14}CH_3$ from S-adenosylmethionine to methionine synthase-cob(II)alamin, or by measuring the formation of a reaction product (i.e., methionine) relative to a control sample (see, e.g., page 34, line 6, through page 35, line 14).

The specification also teaches assays for determining whether the nucleic acid molecule having a polynucleotide sequence that is complementary to SEQ ID NO: 1, SEQ ID NO: 41, SEQ ID NO: 43, SEQ ID NO: 45, or SEQ ID NO: 47, as is recited in present claims 41, and claims dependent therefrom, is capable of causing a decrease in the expression of a methionine

synthase reductase polypeptide. The specification at page 35, line 15, through page 36, line 20, describes the use of an enzyme-linked immunosorbant assay (ELISA) for determining whether a compound (e.g., an antisense nucleic acid molecule) is able to modulate the level of expression of a methionine synthase reductase polypeptide. Page 37, lines 1-18, of the specification describes the use of a quantitative PCR assay for determining the ability of a compound to modulate the level of a methionine synthase reductase polypeptide (i.e., by detecting the amount of mRNA levels in a sample). Therefore, for all of the reasons provided above, the full scope of present claims 1, 4, 36, and 41, and claims dependent therefrom, is enabled and the rejection of these claims for lack of enablement should be withdrawn.

The Examiner also rejects claim 47, stating that the specification fails to provide enablement for a polynucleotide "encoding a mammalian methionine synthase reductase which comprises any consensus binding site for FAD, FMN and NADPH" (Office Action, p. 13). Applicants have amended claim 47 to recite that the binding site comprises any one of SEQ ID NOs: 25-40. Therefore, this rejection should be withdrawn as well.

Because Applicants' disclosure provides several human methionine synthase reductase nucleic acid molecules and considerable guidance with respect to methods that can be used to identify additional methionine synthase reductase nucleic acid molecules (using both structural and functional characteristics), Applicants submit that the full scope of present claims 1-5, 36-38, 41-43, 45-47, and 52 is enabled and that the rejection of these claims under 35 U.S.C. § 112, first paragraph, should be withdrawn.

CONCLUSION

Applicants submit that the claims are in condition for allowance, and such action is respectfully requested.

Enclosed is a petition to extend the period for replying for three months, to and including March 3, 2004.

If there are any charges, or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

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Date: 2 March 2004 For _____

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